UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,720	12/20/2001	David S. Thomson	1/1180	3886

28501 7590 08/10/2004

BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877

EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 08/09/04 RA

Office Action Summary	Application No.	Applicant(s)	
	10/029,720	THOMSON ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/11/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group IV, claims 15-18, in the reply filed on 07/06/2004, is acknowledged. Therefore, claims 1-14 and 19-21 are withdrawn from consideration and claims 15-18 are examined in this action.

Specification

The disclosure is objected to because of the following informalities: There appear to be minor grammatical or typographical errors in the specification; on page 2, bottom of the page; the term "heeling" should read "healing". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claim 15 recites, "A method for screening for a dissociated glucocorticoid receptor (GR) antagonist... ". As written the claim's metes and bounds are not determinable, because it is not clear whether the transitive verb "dissociated" is directed to the antagonist or the GR. The term does not appear to be defined in the specification. For example, it is understood in the art that a GR occurs in the cell cytoplasm as part of a multi-protein complex, whereby

glucocorticoid binding to GR causes GR to release from this complex, i.e. GR "dissociates". It is also noted that in the art glucocorticoids can be referred to as "dissociated glucocorticoids". However as written, it is unclear whether the claim is directed to a "dissociated" antagonist, or "dissociated" GR. Therefore it is unclear how the claim should be interpreted in determining the invention's metes and bounds. It would be remedial to move "dissociate" immediately before "antagonist" to clarify this ambiguity.

The claim also recites the term, "sensitive" when relating glucocorticoid and target gene, where the term "sensitive" does not appear to be specifically defined in the specification. The specification merely repeats the same phrase as is claimed. (e.g. Spec. p. 4, ¶ 1, last sentence). It is understood from the entire disclosure, that the target gene undergoes transactivation or transrepression in response to GR (i.e. transactivation or transrepression is GR mediated). However, as written, the term "sensitive" is vague, indefinite and a relative term, thus makes indeterminable the invention's metes and bounds.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claim 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Vanden Berghe et al. (Mol. Pharm. 1999 Oct; 56:797-806; see whole document).**

The claim is directed to a method of screening for an glucocorticoid receptor (GR) antagonist where the candidate substance is contacted with a GR, binding of the substance to GR is determined, the substance is selected based on having some affinity for the GR and the substance is further selected based on having an antagonist transactivation and not transrepression activity. The determination of binding activity is interpreted as broadly as reasonable to mean direct or indirect determination. The method is interpreted to be directed to selecting an antagonist having an inhibitory effect, on an otherwise GR-mediated expression of a GR inducible target gene. Put another way, the method selects a ligand that inhibits expression of the target gene. Additional embodiments are directed to the GR-mediated transactivation stimulates a mouse mammary tumor virus promoter (MMTV) in HeLa cells. Further embodiments are directed to GR-mediated transrepression of a gene having cytokine activity.

Vanden Berghe et al. teach a method for identifying (i.e. selecting) antagonist that bind GR in order to separate antagonist-dependant transactivation and transrepression of GR-responsive target genes so as to identify better tolerated drugs. (e.g. p. 798, col. 1, ¶ 3). More particularly, a host of various antagonist candidates (i.e. synthetic glucocorticoids or GCs) are tested and selected for based on their ability to bind GR and inhibit TNF-induced IL-6 secretion in HeLa cells. (Id.; p. 801, Fig. 2; p. 803, Fig. 4). Binding is determined indirectly through the actual outcome of the experiments, i.e. reporter gene expression induction or reduction. Furthermore, the GR-responsive target gene is luciferase, which is under control of an MMTV promoter. (e.g. p. 798, col. 2, ¶ 3 middle; p. 803, col. 1, Fig. 4). In addition, the GR-mediated transrepression of cytokine genes is assayed, such as for IL-6. (e.g. p. 798, col. 2, under

"Cytokines"; p. 803, col. 2, under "Dissociated GCs with Anti-Inflammatory potential Inhibit IL-6", Figs. 5-6). In sum, Vanden Berghe et al. anticipate the rejected claims.

3. Claim 15-18 is rejected under 35 U.S.C. 102(b) as being anticipated by Vayssiere et al. (Mol. Endoc. 1997; 11(7):1245-1255).

As noted above, the invention is directed to a method for selecting an antagonist that inhibits GR-mediated expression of a target gene. (*See supra*, under Rejection No. 2 for further discussion of claim interpretation). With respect to IL-8 induction in THP1 cells in response to lipopolysaccharides (LPS), it is noted that an intrinsic inflammatory response to LPS involves production of IL-1β, as well as IL-8.

Vayssiere et al. teach a method for selecting GCs that dissociate transactivation and transrepression. (e.g. Abstract). More particularly, a series of substances are tested for GR binding, transactivation effect on a GR-responsive target gene and AP-1 transrepression. (e.g. p. 1249, Table 1, including legend; *See also*, p. 1246; teaching that the GR ligand binding domain mediates AP-1 transrepression). The library of substances is screened to find ligands that inhibit AP-1 activity without inducing agonistic activity. (e.g. p. 1246, under Results; p. 1249 last ¶ bridging to p. 1250). In addition, GR-mediated activation of tyrosine transaminase (TAT) is assayed in regard to various candidate antagonist substances, in transfected rat hepatoma cells (i.e. HTC cells). (e.g. p. 1250, Fig. 4; p. 1253 col. 2 under TAT Assay). Furthermore, ligands are assayed for GR-mediated transrepression in inhibiting production of IL-1β in response to LPS. (e.g. p. 1253, col. 2, under Assay of IL-1β Secretion). The inflammatory response to LPS involves production of a cascade of IL factors. Put another way, the cells expression IL-1β

inherently express IL-8 as well. (*See*, Matsukawa et al. Inflamm. Res. 1998; 43(3):137-44; Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to show that a characteristic not disclosed in the reference is inherent. *See* MPEP § 2131.01. The additional references merely shows that LPS induces production of various IL factors, including IL-1β and IL-8). In sum, Vayssiere et al. anticipate the rejected claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER